REMARKS

The Office Action mailed March 18, 2009 has been carefully considered and the following response prepared. Claims 3-7, 9, 10, 16, 18, 21 and 25-33 are pending in the application.

Claims 10, 16, 25 and 30-32 have been amended. Support for the amendment to claim 16 can be found throughout the specification and in particular at page 7, lines 19-20. Support for the amendments to claims 10, 25, and 30-32 can be found throughout the specification and in particular at page 2, line 28 – page 3, line 3, and page 5, lines 13-15. No new matter has been added.

REJECTION UNDER 35 USC 102(b)

At pages 2-3 of the Office Action, the Examiner rejected claims 16 and 28-29 under 35 USC 102(b) as anticipated by Gaynor et al., U.S. Patent 5,904,924. The Examiner stated that Gaynor et al. teaches a nutritional powder formulation comprising 250 mg glutamine and green tea extract, and that when added to 10 or 20 ounces of water, the glutamine content is 0.825 g/1000 ml in 10 ounces of water, or 0.422 g/1000 ml when added to 20 ounces of water.

Applicants traverse this rejection. Claim 16 has been amended to state that component b), at least one NO donor or precursor thereof which is selected from the group consisting of glutamine, and precursors of glutamine in the form of a di- or tripeptide containing glutamine, or the physiologically tolerated salts or combinations thereof, is present in the formulation in the amount of 1 – 150 grams/1,000 ml. Claim 28 depends from claim 16. Claim 29 has been canceled without prejudice.

Gaynor et al., U.S. Patent 5,904,924, discloses a nutritional powder that is a blend of natural food and herbal products which is compounded in dry form into a green nutritional powder mixture which is readily soluble in a fluid for ingestion by humans. The contents of the nutritional powder mixture are set out in the table at columns 4 and 5 of the patent. The mixture contains a number of phytonutrients, including soy lecithin, soy lectin and rose hips; herbs and

phytochemicals, including grape seed extract, Japanese green tea, and soy isoflavones; alpha amino acids, including carnitine and glutamic acid; algae, such as spirulina, and Irish moss; green grass juice powders, and other nutrients. The mixture contains 250 mg glutamine per 969 gram serving, and 40 mg Japanese green tea (standardized to 7.5% catechins predominantly as (-) epi-gallocatechin gallate (EGCG)). The '924 patent states at column 4, that a 969 gram serving of the mixture can be combined with approximately 10 to 20 ounces of water to provide a palliative nutritional drink.

Gaynor et al. does not anticipate amended claim 16, or claim 28. A nutritional drink prepared by dissolving 969 grams of the nutritional powder mixture in ten to twenty ounces of water would contain 0.825 grams/1000 ml (dissolved in ten ounces of water) to 0.422 grams glutamine/1000 ml (dissolved in twenty ounces of water), which is less than the amount specified in amended claim 16. In amended claim 16, component b), at least one NO donor or precursor thereof which is selected from the group consisting of glutamine, and precursors of glutamine in the form of a di- or tripeptide containing glutamine, or the physiologically tolerated salts or combinations thereof, is present in the formulation in the amount of 1 – 150 grams/1,000 ml. Gaynor et al. thus does not anticipate claims 16 and 28.

Withdrawal of this section 102(b) rejection is respectfully requested.

REJECTION UNDER 35 USC 103

At pages 3-4 of the Office Action, the Examiner rejected claims 16, 18-19 and 28-29 under 35 USC 103 as *prima facie* obvious over Gaynor et al., U.S. Patent 5,904,924 in view of Itou et al., JP 409012454. The Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to include theanine in the composition taught by Gaynor et al., since theanine is part of green tea (a component of Gaynor's composition) and theanine would enhance the flavor of the beverage taught by Gaynor et al.

Applicants traverse this rejection.

Amended claim 16 is directed to a formulation for gastrointestinal administration to a surgical patient before surgical procedures to reduce the risk of postoperative ischemia-reperfusion injury or to avert such a risk comprising a composition comprising a) green tea extract and b) 1 – 150 grams/1,000 ml of the formulation of at least one NO donor which is a substrate of NO synthetase, or a precursor of this NO donor, wherein the NO donor and precursor are selected from the group consisting of glutamine, and precursors of glutamine in the form of a di- or tripeptide containing glutamine, or the physiologically tolerated salts or combinations thereof. Claims 18-19 and 28 depend from claim 16. Claim 29 has been cancelled without prejudice.

A *prima facie* case of obviousness requires the following: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Gaynor et al. was discussed above.

Itou et al., JP 409012454, discloses a composition for increasing learning efficiency, which composition contains, as an active ingredient, theanine, one of the amino acids which is found in green tea in large amounts, and is a major contributor to the good taste of green tea.

Claims 16, 18-19 and 28 are not *prima facie* obvious in view of the combined teachings of Gaynor et al. and Itou et al. The combined teachings of Gaynor et al. and Itou et al. do not disclose or suggest a formulation containing component b) of claim 16, 1 – 150 grams/1,000 ml of the formulation of at least one NO donor which is a substrate of NO synthetase, or a precursor of this NO donor, wherein the NO donor and precursor are selected from the group consisting of glutamine, and precursors of glutamine in the form of a di- or tripeptide containing glutamine, or the physiologically tolerated salts or combinations thereof.

The combined teachings of Gaynor et al. and Itou et al. do not disclose or suggest all of the limitations of the formulations of claims 16, 18-19 and 29. The formulations of claims 16, 18-19 and 29 are therefore not *prima facie* obvious in view of Gaynor et al. and Itou et al.

Applicants submit that a *prima facie* case of obviousness has not been established, and that the present rejection is improper and should be withdrawn. Withdrawal of this section 103 rejection is respectfully requested.

REJECTION UNDER 35 USC 103

At pages 5-12 of the Office Action, the Examiner rejected claims 3-7, 9-10, 16, 18-19, 21 and 25-33 under 35 USC 103 as obvious over Zhong et al., Schneider et al. (U.S. Patent 6,656,608), Sherrat et al. (U.S. Patent 6,423,349), Furst et al. (1990), Schneider et al. (U.S. Patent 5,902,829) and Yokozowa et al. (2002). The Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the green tea extract taught by Zhong et al. and the glycine and glutamine taught by Schneider et al. '608 and Sherratt et al., and Schneider '829, respectively, to obtain a composition which would be useful for treating preoperative patients to reduce the risk of ischemia reperfusion injury. The Examiner further alleged that the administration time taught by the instantly cited references would render obvious the instantly claimed administration which takes place less than twenty-four hours before surgery.

Applicants traverse this rejection. Claims 10 and 25 has been amended to state that administration of the composition begins less then twenty-four before a surgical procedure. Claims 30-32 have also been amended to state that administration of the composition begins less than twelve, six or three hours before a surgical procedure, respectively.

Applicants' remarks concerning Zhong et al., Schneider et al ('608 patent), Sherratt et al., Schneider et al. ('829 patent), and Yokozawa et al. in the response filed November 24, 2008 are hereby incorporated by reference. Furst et al. discloses the use of glutamine-containing dipeptides in parenteral nutrition.

In the Office Action, at pages 8-9, the Examiner remarked that administration times taught by the instantly cited references would render obvious the instantly claimed administration which takes place less than twenty-four hours prior to surgery because the references teach administration which begins before surgery. The Examiner's remarks continued by alleging that administration that begins at any time prior to surgery and continues until surgery would be taking place less than twenty-four hours prior to surgery, as instantly claimed.

To clarify the claimed methods, claims 10, 25, and 30-32 have been amended to state that administration of the composition comprising glutamine and at least one NO donor begins less than twenty-four hours before a surgical procedure (claims 10 and 25), or less than twelve, six or three hours before a surgical procedure (claims 30-32).

The claimed compositions and methods are not obvious in view of Zhong et al., Schneider et al. ('608 patent), Sherrat et al. ('349 patent), Furst et al. (1990), Schneider et al. (U.S. Patent 5,902,829) and Yokozowa et al. (2002). None of the cited references, alone or in any combination, disclose or suggest the claimed methods of averting or reducing the risk of postoperative complications wherein a composition comprising a) green tea extract and b) at least one NO donor, or precursor thereof selected from the group consisting of glutamine, and precursors of glutamine in the form of a di- or tripeptide containing glutamine, or the physiologically tolerated salts or combinations thereof, is gastrointestinally administered to a surgical patient beginning less than twenty-four hours before a surgical procedure. Nor is there any disclosure or suggestion of administration of such composition beginning less than twelve hours, less than six hours, or less than three hours before a surgical procedure, as claimed in claims 30-32, respectively.

Applicants have surprisingly found that administration of the claimed composition to a surgical patient beginning less than 24 hours before a surgical procedure averts or reduces the risk of postoperative complications. The Declaration of the inventor Dr. Heinz Schneider, previously submitted, presented experimental data showing that green tea extract together with

glutamine ameliorates ischemia-perfusion injury, whereas a solution of glutamine in combination with other antioxidants did not provide protection against postoperative complications.

There is no suggestion or motivation to modify the cited references by adjusting the time of administration such that administration of the composition comprising green tea extract and at least one NO donor or precursor thereof begins less than 24 hours before a surgical procedure. The periods of administration of Zhong et al., the Schneider '608 patent, Sherratt et al., and the Schneider '829 patent, whether before surgery or after, are much longer than the periods recited in claims 10, 25, and 30-32.

Persons skilled in the art looking to administer a composition comprising green tea extract and at least one NO donor or precursor thereof would be more likely to adjust the time of administration of such a composition to a longer time period before surgery than a shorter period of less than 24 hours as recited in the claimed methods. Zhong et al. administered green tea extract for a period of five days before surgery. The Schneider et al. '608 patent suggests administering the dietary supplement for three days or longer before surgery, generally three to six days before surgery. In Sherratt et al. the compositions are administered to patients 1-2 days prior to and/or after elective surgical procedures. The Schneider et al. '829 patent discloses that the medicament is administered at least one day prior to surgery, but can be initiated between 3-10 days prior to surgery.

Based on the disclosures of the cited references, the skilled person would thus most likely select a starting time for administration of the composition near the five days prior to surgery disclosed in Zhong et al. to have a better chance of obtaining a reduction in ischemia/reperfusion injury from a composition containing green tea extract and glutamine, or green tea extract, glutamine and glycine. There was no reasonable expectation of success for adjusting the time of administration of such a composition to a period less than twenty-four hours prior to a surgical procedure. The time periods prior to surgery shown in the cited prior art are days longer than the period recited in the claimed methods, and there is no disclosure or suggestion in any of the cited

references that a time period beginning less than twenty-four hour prior to surgery would be effective.

The timing of administration of the composition recited in the claims of the present application is therefore not merely a matter of routine optimization. As discussed in the specification at pages 1-2, what is common to all of the treatments for reducing ischemia-reperfusion injury, cited in the present rejection and/or discussed in the specification, is that they must be performed for at least one day, ordinarily a plurality of days, before a surgical procedure. For patients with an acute need for surgery on an emergency basis, the time available is frequently insufficient to achieve a satisfactory result with known methods. The claimed methods and formulation overcome this drawback of known methods. Applicants discovered, contrary to the combined teachings of the cited references, that administration of a composition comprising a) green tea extract and b) at least one NO donor or precursor thereof, wherein the NO donor and precursor are selected from the group consisting of glutamine, and precursors of glutamine in the form of a di- or tripeptide containing glutamine, or the physiologically tolerated salts or combinations thereof, beginning less than twenty-four hours before a surgical procedure, averts or reduces the risk of postoperative complications. The claimed methods and formulations are especially useful for the support of emergency patients, and other patients in which only a short period, such as a few hours, is available before a surgical procedure.

Claims 3-7, 9, 10, 16, 18-19, 21, 25-28 and 30-33 are not obvious in view of the combined teachings of Zhong et al., the Schneider et al. '608 patent, Sherrat et al., Furst et al., the Schneider et al. '829 patent and Yokozowa et al. Withdrawal of this section 103 rejection is respectfully requested.

In view of the above, the present application is believed to be in a condition ready for allowance. Entry of the amendments to the claims is requested as these amendments place the claims in condition for allowance, or at least better form for appeal. Reconsideration of the application is respectfully requested and an early Notice of Allowance is earnestly solicited.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 09600-00031-US from which the undersigned is authorized to draw.

Dated: June 18, 2009

Respectfully submitted,

Electronic signature: /Liza D. Hohenschutz/
Liza D. Hohenschutz
Registration No.: 33,712
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P. O. Box 2207
Wilmington, Delaware 19899-2207
(302) 658-9141
(302) 658-5614 (Fax)
Attorney for Applicant

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